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Structural basis of DNA gating by gyrase and topoisomerase IV and its inhibition by antibacterial therapeutics

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Gyrase and topoisomerase IV (topo IV) are bacterial type II topoisomerases that regulate cellular DNA topology and are key targets of antimicrobial therapeutics. The enzymes share close mechanistic and architectural similarity notably a DNA gating mechanism that involves the formation of a covalent enzyme-DNA complex known as the 'cleavage complex'. Antibacterial fluoroquinolones and quinazolinediones stabilize the cleavage complex triggering cell death. To gain insight into the reaction cycle and drug action and resistance, we solved the first crystal structures of drug-DNA cleavage complexes with several different quinolones. We present structures for topo IV and gyrase revealing details of the cleaved DNA gate and drug binding pockets. Recently, we have also solved structures for the three-gate 'open clamp' state of topo IV, a key intermediate that suggests a mechanism for how DNA is captured and transported through the enzyme complex. Our studies provide new insights on how DNA is manipulated by these complex molecular machines to mediate DNA supercoiling and chromosome segregation.

Biography

Larry Mark Fisher has obtained his PhD in Chemistry from Harvard University and was a Damon Runyon Walter Winchell Cancer Fellow at NIH working with Dr Martin Gellert. He is the Dean of Research at St George's, University of London. He has published more than 100 papers on DNA topoisomerases and DNA supercoiling in bacteria, yeast and human cell systems.

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